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Itraconazole Formulation Studies of the Melt-Extrusion Process with Mixture Design

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ABSTRACT

Itraconazole is a poorly water soluble compound. One method to increase the aqueous solubility of itraconazole is through formation of a solid dispersion. The purpose of this study is to develop a 40% w/w itraconazole formulation through solid dispersion formation, using hydroxypropyl-β-cyclodextrin (HP-β-CD) and hydroxypropylmethylcellulose (HPMC) as mixture components. The solid dispersion was obtained by melt-extrusion using a twin-screw corotating melt extruder. A D-optimal mixture design was applied for the development of the optimal itraconazole formulation. The itraconazole fraction varied between 20% w/w and 50% w/w in the mixture design and the HPMC and HP-β-CD fractions varied between 10% w/w and 60% w/w. The itraconazole formulation was optimized by producing clear extrudates, minimizing the torque, and maximizing the glass transition temperature and the apparent itraconazole solubility in 0.1 N HCl. Regression models were developed for the torque, glass transition temperature, and apparent solubility of itraconazole. High itraconazole fraction in the mixture promoted a better melt processing (minimizes torque). High HPMC fraction (>33% w/w) resulted in clear extrudates, indicating a solid dispersion and resulted in high glass transition temperature of the melt. High HP-β-CD fraction resulted in increased apparent itraconazole solubility in 0.1 N HCl. The optimal itraconazole formulation consisted of 45% w/w HPMC and 15% HP-β-CD w/w.

Key Words: Melt-extrusion process; Extrudates; D-optimal mixture design; Glass transition temperature; Itraconazole; Solubility.

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1.0. INTRODUCTION

Itraconazole is an antifungal agent used both orally and intravenously.[1–3] The oral bioavailability is limited by its poor aqueous solubility of itraconazole,[1] meaning that apparent solubility must be increased if bioavailability is to be optimized. Possible solutions include dissolving the drugs in micelles by adding surfactants or preparing micro-emulsion,[4] forming inclusion complexes with other molecules such as cyclodextrins,[5,6] forming nanoparticles of the drugs,[7] or embedding the amorphous drugs[8] in a polymer matrix.[9,10] Embedding the drug homogeneously in a polymer matrix produces a solid dispersion. Solid dispersions can be prepared in two ways: the solvent method[11] and the hot melt method.[10] The solvent method uses an organic solvent wherein the drug and appropriate polymer are dissolved and then (spray) dried. The major drawbacks of this method are the use of organic solvents and the batch mode production process. The hot melt method uses heat in order to disperse or dissolve the drug in an appropriate polymer. The melt-extrusion process is an optimized version of the hot melt method. The advantage of the melt-extrusion approach is lack of organic solvent and continuous production process. As the melt-extrusion is a novel pharmaceutical technique, the literature dealing with it is limited.[9,12–15] The technical set-up and equipment of the melt-extrusion process used in this study are described by Baert, Peeters, and Verreck.[16] In this study a mixture of itraconazole, hydroxypropyl-β-cyclodextrin (HP-β-CD), and hydroxypropylmethylcellulose (HPMC) was extruded, in order to enhance the apparent water solubility of itraconazole.

Cyclodextrin is a toroidal-shaped molecule with hydroxyl groups on the outer surface and a cavity in the center.[17] Cyclodextrin improves drug solubility in water by forming an inclusion complex with the drug. The complex formation between cyclodextrins and drugs has been investigated extensively.[5] Miyake et al.[6] have shown that HP-β-CD forms a 1:1 and 2:1 complex with itraconazole in solution at pH 2.0. It is known that water-soluble polymer interacts with cyclodextrin and drug in the course of complex formation to form a stabilized complex of drug and cyclodextrin cocomplexed with the polymer. This complex is more stable than the classic cyclodextrin-drug complex.[17] As HPMC is water-soluble, using this polymer with HP-β-CD in the melt is expected to improve the apparent aqueous itraconazole solubility.

Baert, Peeters, and Verreck[16] extruded itraconazole with HP-β-CD and noted that the dissolution rate of itraconazole in gastric acid was improved significantly. In this study only a binary melt mixture was examined. Baert et al.[16] extruded itraconazole with HPMC and noted an increased release of itraconazole from the immediate release tablet. The marketed itraconazole capsules (Sporanox™) consist of coated beads of itraconazole with HPMC (2:3 w/w),[19] which requires a complex fluidized bed granulation process.

The goal of this study is to develop an alternative formulation for the marketed itraconazole formulation with much simplified melt-extrusion process, showing optimal responses for the glass transition temperature of amorphous itraconazole and the apparent itraconazole solubility in 0.1 N HCl.

Mixture design is an appropriate method for finding the optimal formulation.[20] As constraints were applied on the excipients, a D-optimal design was appropriate in this study.[21,22]

2.0. MATERIALS AND METHODS

2.1. Materials

Itraconazole and Hydroxypropyl-β-cyclodextrin (HP-β-CD) were obtained from Janssen Research Foundation (Janssen Chemica, Geel, Belgium). Hydroxypropylmethylcellulose 5 cps (HPMC) was purchased from Dow (Dow, Midland, MI).

2.2. Melt-Extrusion Process

Preliminary Experiments

Preliminary runs were performed on a twin-screw corotating APV MP 19 melt extruder (APV MP 19 PH25:1, APV Baker Limited, Newcastle-under-Lyme, UK) for the determination of the lower and upper constraints of the polymers and itraconazole. Several mixtures of itraconazole and HP-β-CD (Table 1) were extruded. The screw extruder had an L/D ratio of 25 (L is length and D is diameter of the screw). The screw configurations were infinite and were the same as used by Baert and Verreck.[16] The corotating screw extruder forced the viscous melt through a die with a diameter of 3.0 mm. A 500 g powder mixture of appropriate weights of itraconazole and HP-β-CD was blended in a Kenwood blender for 15 min. The temperature of the first zone was

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Table 1. The solubility and extrudate aspect of the preliminary experiments with HP-β-CD and itraconazole.

Relative fractions (w/w)		Solubility (mg/mL)		
HP-β-CD	Itraconazole	Physical	Melt	Extrudate aspect
0	1	0.012		
0.5	0.5	0.21	0.24	Turbid, white
0.75	0.25	1.28	0.65	Turbid, white
0.83	0.17	2.43	2.00	Clear, light brown
0.91	0.09	6.05	> 39.3	Clear, brown

set to 50°C. The temperature of the other zones was set to 250–255°C, as the melting point of HP-β-CD was ± 259°C. The screw speed was set to 400 rpm and the feed rate was set to 10 rpm (0.4–1.1 kg/h, depending on the density of the powder blend). A 100 g extrudate was sampled, milled in a Moulinex coffee grinder, and the < 150 μm sieve fraction was retained. DSC analyses and solubility and mass spectral analyses were subsequently performed on the sieve fraction. Mass spectrometry was performed using a mass spectrometer of Micromass, type AutoSpecq (Micromass, Manchester, UK). The samples were injected at a flow rate of 10 μL/min and at a concentration of approximately 50 ng/mL using a syringe pump (Harvard, Kent, UK). Ionization was performed using the electrospray negative ionization mode and a scan was recorded between 1000 and 1800 Da with a resolution of 1000. Data were collected through multiple channel analysis (MCA).

Mixture Design Experiments

The results of the preliminary experiments were used for the construction of a mixture design (see Discussion). The experimental work of the mixture design was performed on a twin-screw corotating APV MP 20 melt extruder (APV MP 20 PH25:1, APV Baker Limited, Newcastle-under-Lyme, UK), which is a more modern version of the melt extruder used in the preliminary experiments. The same screw extruder configurations were used as in the preliminary experiments and the die diameter was also 3.0 mm. One kilogram powder mixture was prepared by blending the appropriate weights of itraconazole, HP-β-CD, and HPMC in a Kenwood planetary blender for 15 min. The blended powder mixture was placed in the feeder of the melt extruder. The feed rate was set to 1 kg/min. A screening run was performed in order to define appropriate barrel temperature and screw speed that would result in acceptable melt processing (torque < 50% and barrel pressure < 15 bar). As the runs in the mixture design have different composition, the optimal temperature and screw speed will also be different for each run. The effect of the process parameters on the extrudate properties has not been investigated much. Henrist and Remon[14] investigated the effect of melt process parameters on the extrudate. They found that the feed rate, the screw speed, and the barrel temperature affected the dissolution behavior of theophylline. Based on this study, it was decided to run all the experiments at constant process settings.

Since the melt viscosity depends on the process conditions and the powder composition, the effect of each component on the torque can be investigated given constant process conditions. Therefore, the process conditions must be sufficient for all the runs in the design to be extruded. The screening experiment showed that a barrel temperature of 244°C, a screw speed of 300 rpm, and a feed rate of 1 kg/h resulted in acceptable torque and barrel pressure. At these settings, the residence time of the powder blend in the melt extruder was about 5 min. The extrudate aspect was also acceptable. These settings were used for the experimental work of the mixture design. When the desired process settings were constant for 10 min, a 100 g sample was collected in a stainless steel bucket and air-cooled. The collected strands were sampled and processed for DSC analysis and the apparent solubility determination.

2.3. Extrudate Evaluation

DSC Analyses

The sieved fraction absorbed moisture, due to the hygroscopic property of HP-β-CD. It is well-known that moisture affects the Tg of glasses.[8,23]

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To minimize the effect of moisture on the Tg, a 1 g sieve fraction was vacuum-dried (Lyovac GT2, Steris, Germany) for 72 hours at room temperature and at $6 \cdot 10^{-2}$ mbar before DSC was carried out.

The DSC analyses were performed on a 5–12 mg dried sample on a Perkin-Elmer differential scanning calorimeter-7 (Perkin-Elmer Ltd., Beaconsfield, UK) from 0°C to 275°C, under a constant nitrogen flow. The heating rate was set to 40°C/min and the cooling rate was set to 20°C/min. The heating rate was rapid in order to enable detection of the glass transition.[24] The Tg was determined at the half heat capacity (Cp) of the glass transition of the material. The peak temperature was considered to be the melt temperature of itraconazole.

Solubility Measurements

An excess of sieved extrudate fraction equivalent to 200 mg itraconazole was added to a 20 ml glass vial with 10 mL 0.1 N HCl and stirred overnight in a 37°C water bath. When all the extrudate was dissolved, more sieved extrudate (50 mg equivalent itraconazole) was added, until a suspension was obtained.

Afterwards the suspension was filtered over a hydrophilic filter (Millipore Millex-LCR hydrophilic PTFE 0.5 μm, Millipore Co., Bedford, MA). The filtrate was diluted to obtain an absorbency between 0.2 and 1.0 measured by an UV spectrophotometer (Hewlett-Packard 8450a, Palo Alto, CA) at $\lambda = 254$ and the concentration in mg/mL was determined.

2.4. Mixture Design

The Designexpert software (Design expert version 6.0, Stat-Ease Inc., Minneapolis, USA) calculated the D-optimal design points in the experimental domain for the proposed model, selected from the candidate runs. It enabled the evaluation of the appropriate regression model. Stepwise regression was performed on the special cubic model, where the interaction coefficient with the largest P-value was consecutively deleted until only significant interaction coefficients (P-value < 0.05) remained in the model. The significant model was used for fitting the response. The lack-of-fit test and a normal probability plot of the residuals were performed in order to evaluate the model and to detect outliers. Contour plots from the significant actual model for the response were drawn for determination of the optimal variable settings.

3.0. RESULTS AND DISCUSSION

3.1. Preliminary Experiments

The preliminary results are summarized in Table 1. Mass-spectral analyses of the sieved extrudate did not show whether the HP-β-CD was degraded due to high temperature. The brown color was more intense at higher HP-β-CD content. Further analyses must be performed in order to investigate the color formation process.

At low itraconazole fraction in the melt, the extrudates were clear, and at high itraconazole fraction the extrudates were turbid-white upon cooling. The clear extrudate indicates that a miscible solid solution was obtained and the turbid extrudate indicates that probably the components were not miscible to each other at that specific composition.[18] DSC analyses of the melts showed a glass transition for the amorphous itraconazole and will be discussed further in the transition temperature section.

The crystalline itraconazole solubility in 0.1 N HCl was 0.012 mg/mL. The apparent itraconazole solubility in 0.1 N HCl increased proportionately with the HP-β-CD fraction in the melt, and the apparent solubility of the physical mixtures was comparable with that of the melt, except at high HP-β-CD fraction in the melt, where the apparent solubility of the melt was significantly higher than that of the physical mixture.

A mixture of HPMC and itraconazole (3:2 w/w) was also extruded, and the extrudate was transparent. The DSC showed a glass transition for amorphous itraconazole. The apparent itraconazole solubility in 0.1 N HCl was 0.37 mg/mL, which was comparable with the same HP-β-CD content in the melt. Baert et al.[18] noted that an extrusion of 1:1 w/w mixture of itraconazole and HPMC resulted in a turbid aspect of the extrudate. This could be due to limited solubility of itraconazole in HPMC, which resulted in a "solid dispersion."

From the preliminary experiments it can be concluded that HPMC yields clear extrudates with high drug loading, but with poor apparent aqueous solubility of itraconazole. HP-β-CD yields clear extrudates with low drug loading and with high aqueous apparent solubility.

As the marketed capsule formulation of Sporanox is composed of beads coated with a mixture of 40% w/w itraconazole and 60% w/w HPMC, therefore a 40% w/w itraconazole formulation based on extrusion with HPMC and HP-β-CD was desirable.

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Therefore the upper limit for HPMC was set at 60% w/w in the mixture. The lower limit for HPMC was set at 10% w/w. In order to compare the effects of HPMC and HP-β-CD on the melt properties, the constraints of HP-β-CD were the same as for HPMC. The upper limit for itraconazole was set to 50% w/w, because higher loading was not necessary and would cause processing problems (dispersion problems, fluid aspect). The lower constraint for itraconazole was set at 20% w/w, where it formed a solid solution with HP-β-CD. Figure 1 shows the constraints of the components in a ternary mixture diagram. The relative fraction of the components in the mixture is normally used in the ternary diagram of a mixture design.[25] For ease of reading, the percentage of the components is used in the ternary diagrams. Because the experimental space is irregular (Fig. 1), the classical mixture design approach such as the simplex design cannot be applied. Therefore a D-optimal mixture design was selected.[21] Because HPMC and HP-β-CD affect the apparent solubility of the itraconazole melt differently, a third order interaction between itraconazole, HP-β-CD, and HPMC was expected. Therefore, the following special cubic model was proposed:

$$Y = \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3 + \beta_{123} X_1 X_2 X_3 \quad (1)$$

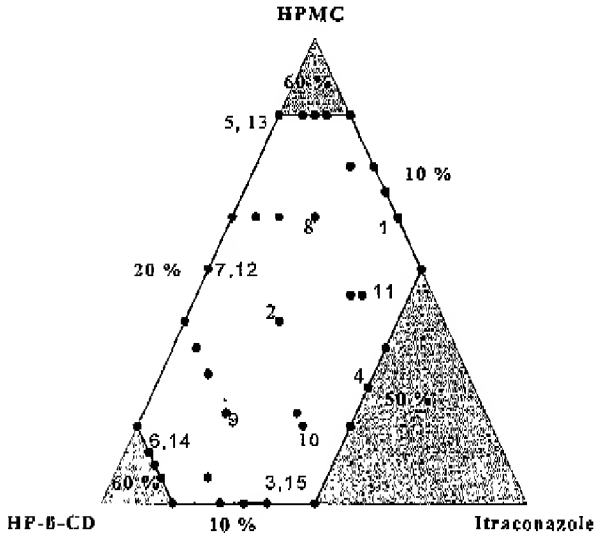

Figure 1. Ternary diagram with the component constraints (in % w/w), the candidate points (circles), and the 15 selected runs for the D-optimal experimental design (denoted by the numbers).

where Y is the response, X_i is the relative fraction of component i in the mixture, and the β_i, β_{ij} and β_{123} are the coefficients.

The candidate points were chosen by the software and were: vertices (6), center and the thirds of the edges (6 + 12), blends in the inner experimental space (12), and overall centroid (1) (Fig. 1). From the 37 candidate points, seven runs were chosen to establish the model, four runs for measuring the lack of fit, and four runs were replicated for the experimental error, so that in total 15 runs were generated. The D-optimal mixture design and response results are shown in Table 2. The visual aspect, the torque, the Tg, and the apparent solubility of itraconazole for each run in the mixture design are shown in Table 2.

3.2. Visual Aspect

The visual aspect of the extrudates is given in Table 2. Runs 3, 4, 6, 9, 11, 14, and 15 resulted in turbid extrudate. The other runs resulted in clear extrudate.

The turbid aspect indicated that a "solid dispersion" was obtained.[18] Such dispersions are not chemically and physically uniform throughout or comprise more than one phase. This could presumably be due to the fact that not all of the itraconazole has dissolved in the melted components. When all the itraconazole has dissolved in the components upon melting, a solution will be formed, which upon cooling may form a solid solution; the solid solution will have a clear aspect. An itraconazole fraction of 43% w/w and high amounts of HP-β-CD in the melt (runs 3, 11, and 15) resulted in turbid extrudates, whereas the same fraction in combination with high amounts of HPMC (runs 1 and 10) resulted in clear extrudates (see Table 2). Presumably a high fraction of HPMC is necessary for dissolving all the itraconazole in the mixture.

As the clear extrudates indicated for a homogenous miscible system upon cooling, it is concluded that the optimal itraconazole formulation (at a fraction of 40% w/w) should contain a high HPMC fraction.

3.3. Torque

Torque is a measure of the viscosity of the melt in the melt extruder. The lower the torque, the lower is the viscosity of the melt. Torque lower than 50% is desired for optimal melt processing of a powder blend.

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Table 2. D-optimal mixture design with the relative fractions of the component, the parameter settings and the responses.

	Components			Response				
						Solubility (mg/mL)		
Run	HPMC	HP-β-CD	Itraconazole	Torque(%)	Tg (°C)	Physical	Melt	Visual aspect
1	0.47	0.10	0.43	34	73.9	0.09	2.68	Clear
2	0.33	0.33	0.33	37	78.0	0.29	4.38	Clear
3	0.10	0.47	0.43	33	69.9	0.35	2.88	Turbid
4	0.25	0.25	0.50	32	69.6	0.17	1.32	Turbid
5	0.60	0.20	0.20	45	103.6	0.28	3.70	Clear
6	0.17	0.60	0.23	42	78.0	0.91	10.53	Turbid
7	0.40	0.40	0.20	49	101.5	0.53	8.30	Clear
8	0.47	0.22	0.32	40	80.7	0.27	3.08	Clear
9	0.22	0.47	0.32	41	77.5	0.61	3.76	Turbid
10	0.37	0.20	0.43	34	74.5	0.19	2.18	Clear
11	0.20	0.37	0.43	34	71.1	0.27	2.11	Turbid
12	0.40	0.40	0.20	48	97.3	0.54	8.35	Clear
13	0.60	0.20	0.20	46	92.3	0.32	4.45	Clear
14	0.17	0.60	0.23	46	80.9	0.69	9.75	Turbid
15	0.10	0.47	0.43	29	69.0	0.49	2.37	Turbid

Tg = glass transition temperature.

Table 2 shows that the torque was always lower than 50%.

All the runs were performed consecutively as given in Table 2, without shutting down the equipment.

Runs 1, 3, 10, 11, and 15 with high itraconazole fraction (43% w/w) in the melt had a significantly lower torque compared with runs 5, 6, 7, 12, 13, and 14 with low itraconazole fraction (±20% w/w) in the melt. At a constant itraconazole fraction in the melt mixture (for example ±20% w/w or 43% w/w), the torque was not significantly affected by HPMC or HP-β-CD (compare the torque of runs 5, 13 and runs 6, 14 respectively of runs 1, 10 and runs 3, 11, and 15). The relatively low melt temperature of itraconazole compared with the high melt temperatures of the polymers explains the plasticizing effect of itraconazole on the melt. The higher the itraconazole fraction in the melt, the more liquid itraconazole is present at the processing temperature, and the more the torque will be decreased.

By stepwise omitting the least significant coefficients of the proposed model in Eq. (1), the following model for the torque was obtained:

$$\text{Torque}\ (\%) = 58.86 \times A + 56.58 \times B + 1.51 \times C \quad (2)$$

where A is relative HPMC fraction, B is the relative HP-β-CD fraction, and C is the relative itraconazole fraction in the melt.

The lack-of-fit test in Eq. (2) was not significant (P-value = 0.56 > 0.05), indicating that the model explained the response very well. The residuals obtained from Eq. (2) were distributed normally. The contour plot of the torque based on Eq. (2) is given in Fig. 2a. The contour plot confirmed the plasticizing effect of the itraconazole on the melt.

3.4. Transition Temperature

DSC analysis is a useful method for the investigation of glass transition temperature.[8,24] Therefore, DSC analyses of each component in the powder blend were performed.

In order to simulate the melt-extrusion process of the individual components in the powder blend, DSC analyses were performed on each component by heating, cooling, and heating again.

The HPMC showed a glass transition at ±138.8°C in the first heating run. The HP-β-CD showed a glass transition at ±175.2°C in the first heating phase and a glass transition at ±259.0°C in the second heating phase, which corresponds with the melting of HP-β-CD. In both DSC graphs an artifact peak at ±55°C was detected. This could be due to the equipment settings at the time of measurements. This peak was not observed when the DSC of the blends was performed. Figure 3 shows the DSC graphs of

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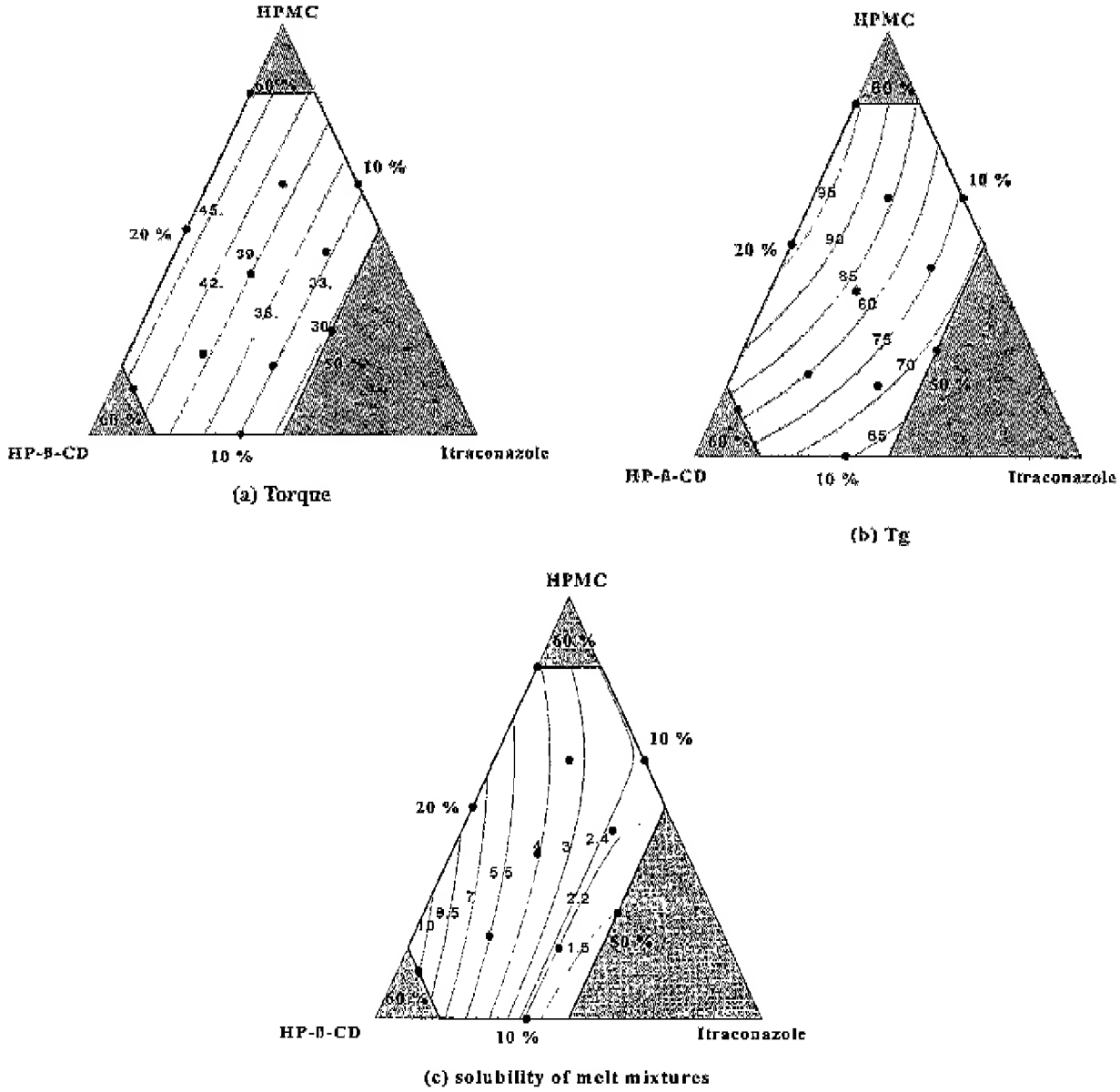

Figure 2. (a) Contour plots of the torque (%), (b) the amorphous itraconazole Tg (°C), and (c) the apparent itraconazole solubility (mg/mL) in 0.1 N HCl obtained from the regression model.

crystalline itraconazole. Crystalline itraconazole was first heated from 25°C to 275°C, resulting in an endothermic melting peak at 175.7°C. The cooling curve shows two small exothermic peaks at 68.9°C and 86.3°C. Afterwards itraconazole was heated again, resulting in a glass transition at 61.8°C and two endothermic peaks at 77.5°C and 93.5°C. These endothermic peaks correspond to the exothermic peaks observed in the cooling phase, shifted to a higher temperature by 7–9°C. This shift is contributed to by the heating/cooling rate of the DSC equipment. It has been suggested by Six et al.[26] that the transitions observed during the cooling and the second heating run of itraconazole represent the formation of glassy itraconazole and a mesotropic mesophase upon cooling from the melt. The shelf-life stability of amorphous drugs is enhanced by storage well below their Tg (> 50K) or by enhancing their Tg

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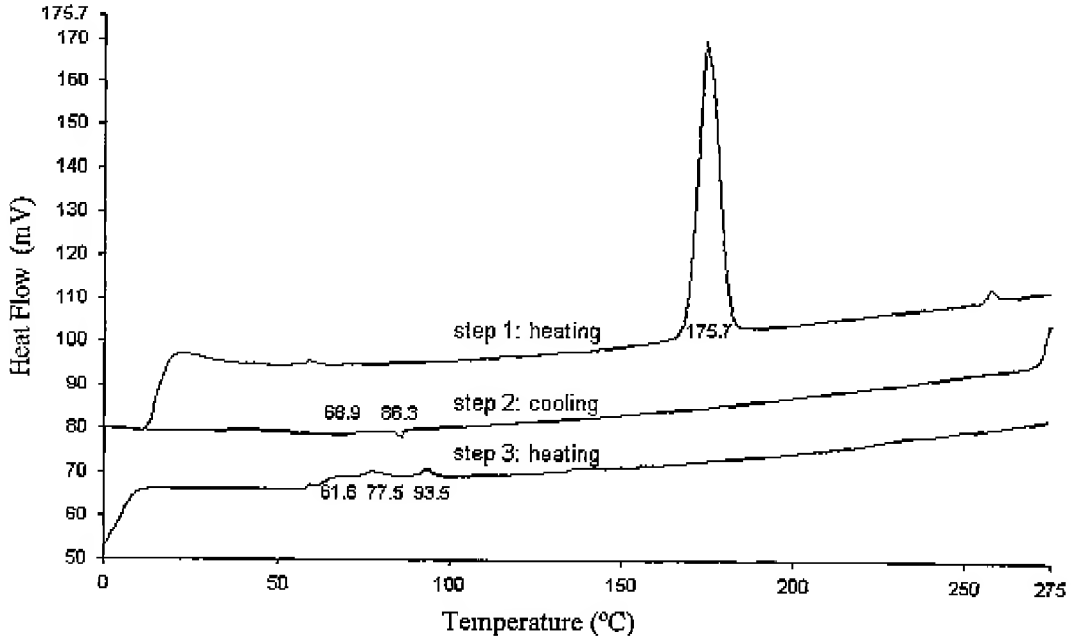

Figure 3. DSC analyses of crystalline itraconazole; heating step (40°C/min) and cooling step (20°C/min).

with high-Tg glass-forming polymers.[8,27] Therefore we wanted to develop an itraconazole formulation with a Tg high enough above room temperature to ensure dosage form stability.

The melting peak of itraconazole at ±175°C and the endothermic peaks at ±78°C and ±94°C were absent in all runs of the mixture design, indicating that crystalline itraconazole was transformed to amorphous itraconazole. Figure 4 shows DSC graphs of melts, with high itraconazole loading and respectively high HPMC loading and high HP-β-CD loading (respectively runs 1 and 3). A relaxation peak was observed after the Tg of itraconazole in these graphs.[24] The DSC graphs of the melts lack the two small endothermic peaks compared with the second heating run of itraconazole. This indicates formation of the monotropic mesophase[26] of itraconazole during melt-extrusion. No degradation peaks were observed at high temperature in the DSC graphs of the runs in the mixture design.

The Tg of itraconazole of all runs is given in Table 2. It is obvious that Tg of amorphous itraconazole depends on the constitution of the mixture. The Tg of itraconazole in the mixtures is significantly higher than for pure amorphous itraconazole (see Figs. 3 and 4, respectively). If there were no molecular interactions, a Tg would be expected near that of pure amorphous itraconazole in the mixtures. The lowest Tg for itraconazole occurred at a high fraction of itraconazole in the melt (runs 1, 3, 4, 10, 11, and 15) and the highest Tg at a high fraction of HPMC and a low fraction of itraconazole (runs 5, 7, 12, and 13). The effect of HPMC on the Tg is obvious when a constant itraconazole fraction in the melt is considered. At a constant itraconazole fraction in the melt mixture (±20% w/w or 43% w/w), the Tg was higher at high HPMC fraction (respectively, runs 5, 13, and 1, 10) compared with high HP-β-CD fraction in the melt (respectively, runs 6, 14, and 3, 11, and 15). Presumably, itraconazole with low Tg (61.8°C) functions as a plasticizer with HPMC, which has a relatively high Tg (138.8°C).

By stepwise omitting the least significant interaction coefficients of the proposed model in Eq. (1), we obtained the following model for the Tg:

$$Tg(°C) = 98.0 \times A + 74.4 \times B + 35.1 \times C + 126.8A \times B \quad (3)$$

where A is relative HPMC fraction, B is the relative HP-β-CD fraction, and C is the relative itraconazole fraction in the melt.

It was found that the interaction between HP-β-CD and HPMC was significant. Probably, some interaction occurred between these two components upon extrusion. Therefore, less HPMC was available

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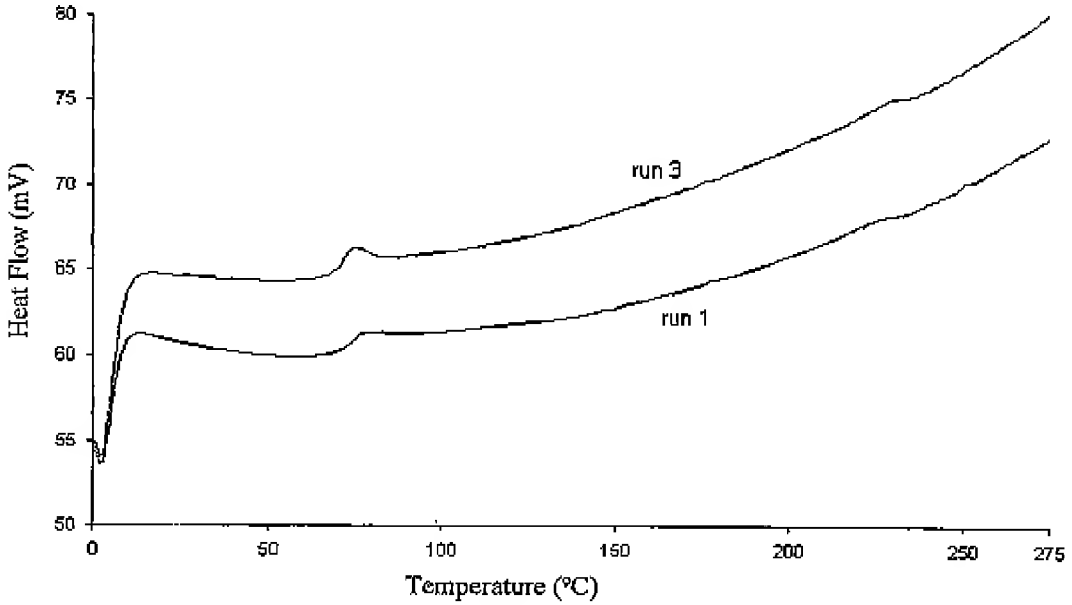

Figure 4. DSC analyses of high itraconazole loading (43% w/w) with respectively high HPMC loading (47% w/w; run 1) and high HP-β-CD loading (47% w/w; run 3). Heating step (40°C/min).

for the itraconazole, which resulted in lower Tg's than was predicted.

The lack-of-fit test in Eq. (3) was not significant (P-value = 0.55 > 0.05), indicating that the model explained the response very well. The residuals obtained from Eq. (3) were distributed normally. The contour plot of the Tg based on the model of Eq. (3) is given in Fig. 2b. It shows clearly that the optimal formulation with an itraconazole fraction of 40% w/w must contain a high fraction of HPMC in order to have high Tg for amorphous itraconazole.

3.5. Apparent Solubility

Table 2 summarizes the apparent itraconazole solubility results of both the physical mixtures and the extruded mixtures in 0.1 N HCl. Runs 1, 5, 10, and 13 with high HPMC fraction in the physical mixtures have a significantly lower apparent itraconazole solubility than runs 3, 6, 11, and 14 with high fraction of HP-β-CD, at comparable itraconazole fraction in the mixtures. These results showed again that HP-β-CD increases the apparent itraconazole solubility in 0.1 N HCl, presumably by complexation.

The effect of melt-extrusion on the apparent itraconazole solubility in 0.1 N HCl was significant; the apparent itraconazole solubility in 0.1 N HCl of the extruded mixtures was approximately five to 30 times higher than that of the physical mixtures. The effect was more pronounced for the clear extrudates (mean was approximately 16 times) compared with the turbid extrudates (mean was approximately nine times).

The effect of HPMC and HP-β-CD on the apparent itraconazole solubility in 0.1 N HCl was only observed at low itraconazole fraction in the melt (compare the solubility of runs 5 and 13 vs. runs 6 and 14 with respectively high HPMC and high HP-β-CD fraction in the melt mixture). This effect disappeared at high itraconazole fraction in the melt mixture; the apparent solubility in 0.1 N HCl was comparable between high HPMC and high HP-β-CD fraction in the melt mixture (compare the solubility of runs 1 and 10 vs. runs 3, 11, and 15 with respectively high HPMC and high HP-β-CD fraction in the melt mixture). Crystalline itraconazole was used in the physical mixtures, which was converted to amorphous itraconazole in the melt after cooling; probably the effect of HPMC and HP-β-CD on the apparent itraconazole solubility in 0.1 N HCl at high itraconazole fraction in the melt mixture was limited, due to high drug loading and the different physical state of itraconazole.

By stepwise omitting the most insignificant interaction coefficients of the proposed model in Eq. (1), we obtained the following model for the solubility of the extruded mixtures:

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Table 3. Predicted and observed responses of the optimal formulation.

	Torque (%)	Tg (°C)	Solubility (mg/mL)	
			Physical mixture	Melt
Predicted (C.I.)	35.6 (33.6–37.6)	77.8 (73.3–82.4)	0.12 (0.052–0.18)	2.48 (1.71–3.25)
Observed	31.0	76.9	0.15	1.70

C.I. = 95% confidence interval.
Optimal formulation is 45% w/w HPMC, 15% w/w HP-β-CD and 40% w/w itraconazole.

$$\text{Solubility (mg/mL)} = -1.15 \times A + 33.35 \times B + 7.20 \times C - 81.37 \times B \times C \quad (4)$$

where A is relative HPMC fraction, B is the relative, HP-β-CD fraction, and C is the relative itraconazole fraction in the melt.

The lack-of-fit test in Eq. (4) was not significant (P-value = 0.111). The residuals obtained from Eq. (4) were investigated for their normal distribution. All the residuals were normally distributed except for the residual of run 9. For run 9 a higher solubility was expected, compared with run 2 with lower HP-β-CD fraction and the same fraction for itraconazole.

The contour plot of the solubility based on the model of Eq. (4) is given in Fig. 2c. This figure showed clearly that itraconazole and HP-β-CD mainly affect the solubility. The higher the itraconazole fraction was, the lower the solubility was. The HP-β-CD effect on the solubility was opposite of itraconazole. The HPMC did not have a pronounced effect on the itraconazole solubility. Figure 2c shows clearly that the formulation with high drug loading (an itraconazole fraction of ±40% w/w) have a robust apparent aqueous solubility; at this itraconazole fraction in the melt it does not depend on the HPMC and HP-β-CD fraction in the melt mixture.

3.6. Optimal Formulation Selection

For optimization of a formulation with an itraconazole fraction of 40% w/w, the following rules were applied: clear extrudates must be obtained, the torque must be minimized, and the Tg and the apparent aqueous solubility must be maximized. The visual aspect results indicated that HPMC fraction must be high (>33% w/w) to obtain clear extrudates. The torque results indicated that neither HPMC nor HP-β-CD level affects the torque significantly. The Tg and the apparent solubility were optimized in Eqs. (3) and (4) respectively, for the itraconazole fraction of 40% w/w and the following mixture was chosen as optimal:

itraconazole: 40% w/w
HP-β-CD: 15% w/w
HPMC: 45% w/w

An experiment was performed for that mixture. The predicted and the observed responses are given in Table 3. The extrudate was clear, as expected from the results in Table 2 and Fig. 1. The observed results were comparable with the expected results. Further formulation development work must be performed in order to investigate the effect of these polymer mixtures on the dissolution release of itraconazole from tablets.

4.0. CONCLUSIONS

This study has shown that melt-extrusion is a promising method to enhance the water solubility of poorly water-soluble drugs, like itraconazole. The visual aspect evaluation of the melt mixtures showed that high HPMC fraction in the melt is preferred, due to clear extrudates formation. The torque evaluation showed that high itraconazole loading in the mixture lowered the torque, which favors a better melt-extrusion process. The evaluation of the itraconazole glass transition temperature in the melt showed that high HPMC fraction was preferred, due to its maximizing effect on it. The apparent solubility of itraconazole in 0.1 N HCl of the mixtures showed that HP-β-CD increased the solubility; however, at high itraconazole loading in the melt mixture, both components, HPMC and HP-β-CD, did not show any effect on the solubility. It is concluded that adding HPMC to the itraconazole and HP-β-CD mixture improved the melt properties significantly.

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